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Review

New expectations in the treatment of anemia in chronic kidney disease☆

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ABSTRACT

The new drugs developed for the treatment of anemia in chronic kidney disease patients, together with their mechanisms of action are reviewed. At present, many of them are already in advanced stages of clinical trials and is expected to be incorporated into the therapeutic arsenal in the coming years. The potential benefits and possible limitations are also described.

Nuevas expectativas en el tratamiento de la anemia en la enfermedad renal crónica

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RESUMEN

Se revisan los nuevos fármacos desarrollados para el tratamiento de la anemia en la enfermedad renal crónica, junto con sus mecanismos de acción. En la actualidad, muchos de ellos se encuentran ya en fases avanzadas de ensayos clínicos y es de esperar que se incorporen al arsenal terapéutico en los próximos años. Se describen las potenciales ventajas y sus posibles limitaciones.

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Introduction

Anaemia is a common complication in advanced chronic kidney disease (ACKD) and its severity increases as kidney function decreases. The introduction of treatment with recombinant human erythropoietin (EPO) (epoetin) three decades ago entirely changed the magnitude of the problem.[1] Table 1 shows the most important events in the treatment of this condition to date.[1–7] Throughout this time, the treatment of anaemia has been based on the use of erythropoiesis-stimulating agents (ESAs), which included epoetin and its analogues, together with the administration of iron by oral or parenteral route.[8] The analogues of erythropoietin include darbepoetin and CERA (continuous erythropoietin receptor activator). Darbepoetin is composed of an EPO that includes two sialic acid molecules, giving it a longer half-life, while CERA is a pegylated EPOβ, with an even greater half-life. In recent years, agents that are biosimilar to epoetin have been incorporated into the therapeutic arsenal, as they are less expensive.

The objective of this review is to raise awareness of the drugs that are currently in different clinical trial phases and that may constitute the basis of treatment for renal anaemia in the coming years. Table 2 shows a simple classification of the different ESAs that we will review.

EPO-mimetic agents

This group includes the peptide molecules that act on EPO receptors in a similar way to endogenous EPO. The first EPO-mimetic on the market is peginesatide (Hematide®), composed of 2 peptide chains of 21 amino acids each, bound to a polyethylene glycol group. Its half-life is estimated at 80 h and it may be administered as a monthly injection; there are no differences between intravenous or subcutaneous routes. This drug was approved by the FDA in 2012, only for use in haemodialysis patients. As it does not require genetic technology for its manufacture, it is a less expensive product than epoetin. Preliminary studies demonstrated other potential advantages such as the absence of immunogenicity, and it may therefore be used in cases of pure red cell aplasia; its greatest efficacy is in patients who are more resistant to other ESAs.

In January 2013, 2 prospective, controlled and randomised studies were simultaneously published for peginesatide in patients with ACKD. The first (EMERALD *Study*) was carried out in the U.S.A. and in Europe. It included patients on haemodialysis and was compared to EPO-α administered 1–3 times/week. The main conclusion was that peginesatide, administered once a month, resulted in haemoglobin levels equivalent to those obtained with epoetin.[6]

The second study (PEARL *Study*) was also developed in the same countries and it compared the efficacy of monthly peginesatide to darbepoetin every two weeks in patients with ACKD without dialysis. The results showed a similar efficacy between the 2 drugs at the end of 52 weeks. However, sudden death was 7 times greater in the peginesatide group, and the mortality rate due to unknown causes was twice as high.[7] Post-marketing data have shown serious hypersensitivity reactions with several deaths,[9] which lead the FDA to withdraw its approval. Therefore, it seems reasonable to assume that in a market as highly competitive as ESAs, the future of peginesatide is poor.

There are other fusion proteins with EPO-mimetic properties currently in the initial study phases.

Table 1 – Most noteworthy events in the treatment of renal anaemia.

1986	First publication with rH-EPO[1]
1990	rH-EPO approved by the EMEA
1998	"Hb normalisation" study[2]
2001	Darbepoetin-α introduced
2006	CREATE and CHOIR studies[3,4]
2007	Pegylated rH-EPOβ approved
2009	TREAT study[5]
2009	"Biosimilars" introduced
2013	First clinical trials with EPO-mimetics[6,7]

Table 2 – Classification of erythropoiesis stimulating agents.

Exogenous EPO
Epoetin and analogues
EPO-mimetic agents
Agents that stimulate endogenous EPO
Prolyl-hydroxylase inhibitors (PHIs)
GATA inhibitors
Agents with other mechanisms of action
Anti-hepcidin agents
Anti-activin agents

Agents that stimulate endogenous erythropoietin

Prolyl-hydroxylase inhibitors (PHIs)

Patients with ACKD have a relative EPO deficiency, and although serum levels may be normal, they are inappropriate for the haemoglobin concentrations they present.[10] Furthermore, there may be hepatic production of EPO, which may be stimulated during episodes of liver disease, as it was demonstrated in patients on haemodialysis many years ago.[11] Moreover, there are EPO-producing cells that remain in the kidneys and other tissues, with a yield sufficient to maintain patients on haemodialysis without anaemia and no need for ESAs. This situation is more common in cases on a long period of renal replacement therapy, in patients with polycystic disease and in cases of liver disease due to hepatitis virus C.[12]

It has been known for many years that the inhabitants of the Andean altiplano have adapted to the state of hypoxia in which they live; in the same way that high altitude affects patients on haemodialysis.[13] Low oxygen pressure induces the expression of the hypoxia-inducible factor (HIF), a transcription factor that regulates the expression of genes involved in erythropoiesis in response to changes in partial oxygen pressure. It is a heterodimeric protein with 2 components: hypoxia-sensitive HIF-α and HIF-β, which is an inactive